3. returned to applicant a copy of the PTO-Form 1449 with the Galardi, Kimura and Lamanna references lined indicating that the examiner do not consider these references.

Applicant responds to the Office Action as follows.

II. Cancelled and Amended Claims

To the extent that they have not already been cancelled from this application, applicant hereby cancels claims 12-13 and 35-36 without prejudice to further prosecution at a later date.

Additionally, applicant hereby cancels claims 9 and 10 without prejudice to further prosecution at a later date.

Claims 7, 15-17 and 38 have been amended.

The claims now pending in this application are therefore claims 7, 15-17 and 37-38.

The amendment to the claims to specify that the botulinum toxin is administered "to an SA node or to an AV node of a heart of a patient with bradycardia" is supported by at least page 31, lines 12-17 of the specification (Example 2). In dependant claims 15-17 "cardiac muscle" has been amended to "heart", because "cardiac muscle " has been amended to "heart" in claim 1. It is well known that the heart is the cardiac muscle and "heart" and cardiac muscle" are synonymous terms.

No new matter or new issues are introduced by these claim amendments.

III. Amended Title

Please amend the title of this application from:

METHOD FOR TREATING CARDIAC MUSCLE DISORDERS BY ADMINISTRATION OF A BOTULINUM TOXIN

to:

INTRAPERCARDIAL BOTULINUM TOXIN TREATMENT FOR BRADYCARDIA

to thereby provide a title more descriptive of the invention as presently claimed.

IV. Rejection of Claims 7, 9-10, 15-17 and 37-38

The Office Action rejected claims 7, 9-10, 15-17 and 37-48 under 35 U.S.C. section 112, first paragraph. Since there are no claims 39-48 in this application applicant believes that a typographical error occurred at the top of page 3 of the Office Action, and that the Office Action intended to reject the pending claims 7, 9-10, 15-17 and 37-38.

The rejection of the claims is on the basis that claims 7, 9-10, 15-17 and 37-38 contain subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention without undue experimentation.

The broadest claim in this application is amended claim 7 which claims:

> "A method for treating bradycardia, the method comprising the step of intrapericardial injection of a botulinum toxin to an SA node or to an

AV node of a heart of a patient with bradycardia, thereby treating bradycardia.

A through reading of the Office Action reveals seven bases (indicated as A to G below) for the section 112(1) rejection of the claims by the Office Action, these seven bases being:

A. the November 5, 2001 Longhurst declaration is stated to be insufficient to overcome the rejection "because the declarant (Dr. Longhurst) states his position without any scientific reasoning or evidence as to why one skilled in the art would successfully be able to treat bradycardia by administering a botulinum toxin to the pericardial pace of a human patient" (page 4 of the Office Action).

B. "...the state of the art is such that no botulinum toxins have been utilized to treat cardiac disorders, such as bradycardia" (page 5 of the Office Action).

C. five "complications have been associated with botulinum toxin therapy" (page 5 of the Office Action). The same alleged "complications" are repeated on pages 7-8 of the Office Action to show what is stated to be an "unpredictability of the effects of botulinum toxin in a subject."

D. the present invention is "unpredictable and complex" since the invention "may not necessarily treat bradycardia" when "any botulinum toxin" is administered by intrapericardial injection (first paragraph on page 6 of the Office Action).

E. "...the specification of the instant application does not disclose any methods or working examples.." (page 7 of the Office Action).

F. "There is no guidance in the specification as to the safe dosage and duration of administration of any botulinum toxin to the cardiac muscle." (page 7 of the Office Action).

G. "the contradictory state of the prior art" (page 8 of the Office Action)

Respectfully, the rejection is in error and should be withdrawn, for at least the following reasons, which are so forth below so as to track the seven bases (A to G) for the section 112(1) rejection made by the Office Action:

A. The November 5, 2001 declaration from Dr. John Longhurst (submitted in response to the July 5, 2001 office action), established Dr. Longhurst as an expert in the field of cardiovascular medicine and specifically in the treatment of cardiac disorders such as bradycardia (see paragraph 5 of the November 5, 2001 declaration).

The Office Action states that the November 5, 2001 Longhurst declaration is insufficient to overcome the rejection because it lacks any scientific reasoning. Respectfully, this is an affront to the declarant who, as shown by Attachment A to his November 5, 2001 declaration, has had no fewer than 174 cardiology and cardiovascular articles published in various medical journals over the last thirty years. Hence, when the declarant states that he has "carefully and thoroughly read" the present application (see paragraph 6 of the November 5, 2001 declaration) and then gives his expert opinion that the present application "provides sufficient disclosure and teaching so that a cardiologist of ordinary skill can successfully treat bradycardia" by practicing the claimed invention (paragraph 6 of the November 5, 2001 declaration), it would appear to be obvious that the declarant has done so by drawing upon his vast and extensive training and experience as a scientist and physician to thereby reach a reasoned scientific conclusion.

It is possible that a reader of the November 5, 2001 declaration, not having in mind the notoriety and vast relevant background of the declarant may view the scientific reasoning of the declarant as being merely implicit in the declaration. Hence, applicant provide attached to this response a further declaration from Dr. Longhurst dated March 27, 2002.

The March 27, 2002 declaration, reiterating what was stated in the November 5, 2001 declaration, states that:

> "1. As I stated in my November 5, 2001 declaration in this patent application, in my opinion this patent application provides sufficient disclosure and teaching so that a cardiologist of ordinary skill can successfully treat bradycardia by administration of a botulinum toxin into an existing pericardial space of a human patient (i.e. in the presence of a pericardial effusion of sufficient magnitude to allow access to the pericardial space) to thereby increase the heart rate of a patient with symptomatic bradycardia."

This statement by the declarant, an expert of long standing in the field of cardiology, including treatment of bradycardia (see paragraph 5 of the November 5, 2001 declaration), is directly contrary to the assertion by the Office Action, through the making of a section 112(1) rejection, that the claimed method for treating bradycardia is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Respectfully, the examiner is not qualified to dispute and is wrong to dismiss as lacking scientific reasoning the statements made by the declarant in paragraph 6 of his November 5, 2001 declaration and in paragraph 1 of his March 27, 2002 declaration.

Nevertheless, to advance prosecution of this application, Paragraph 2 of the March 27, 2002 declaration is presented to explicitly provide the scientific reasoning for the conclusion quoted above and states:

> "2. The conclusion in paragraph 1 above is based on the following

> well known facts: (1) the heart receives sympathetic and parasympathetic innervation (see e.g. page 1, lines 15-16 of the patent application); (2) sympathetic (adrenergic) stimulation of the heart increases heart rate (see e.g. page 1, line 16 of the patent application); (3) parasympathetic (cholinergic/vagal) stimulation of the heart decreases heart rate (see e.g. forth at page 1, lines 17-18 of the patent application); (4) local administration of botulinum toxin causes a reversible inhibition of acetylcholine release from cholinergic nerve terminals (see e.g. page 13, lines 1-6 of the patent application)."

Thus paragraph 2 of the March 27, 2002 declaration sets forth the factual basis for the conclusion in paragraph 1 of the same declaration. Significantly, the factual bases for the scientific reasoning by the declarant are drawn directly from the cited text of the present application.

Based upon the scientific reasoning set forth, the declarant then states that the claimed invention can be practised for the stated purpose:

> 3. Hence it is reasonable to conclude, as set forth at page 22, lines 18-24 of the patent application, that for a patient with symptomatic bradycardia, vagal nerve inhibition and hence an increase in heart rate can be accomplished by administration of botulinum toxin into an existing pericardial space in the presence of a pericardial effusion of sufficient magnitude to allow access to the pericardial space, to thereby increase the heart rate of a patient with symptomatic bradycardia.

Thus, the basis for the maintained section 112(1) rejection, that is that the claims are not enabled because the November 5, 2001 declaration which purports to the contrary lacks scientific reasoning, has been traversed. The declarant is a cardiologist with extensive training and experience in the field of cardiovascular medicine and in his opinion a cardiologist of ordinary skill can successfully practice the claimed invention (paragraph 6 of the November 5, 2001 declaration, and; paragraph 1 of the March 27, 2002 declaration). Additionally, the declarant has supported his opinion with explicit scientific

reasoning, as requested by the Office Action (paragraph 2 of the March 27, 2002 declaration).

Thus, the Longhurst declarations provide conclusive evidence regarding enablement of the claimed invention. Additionally, the declarations must be given considerable weight because they are from an expert in the field of the claimed invention. Furthermore, the declarations are persuasive because the declarant explicitly sets forth the scientific reasoning for his opinion and has reaffirmed his opinion in a second declaration.

Thus, the Longhurst declaration presents admissible expert opinion evidence which rebuts the *prima facie* case of lack of enablement made by the Office Action and the rejection of the claims under section 112(1) should therefore be withdrawn.

B. As the second basis for the rejection of the claims under 35 U.S.C. section 112(1), and after noting that botulinum toxin has been used therapeutically in many thousands of humans since about 1978, the Office Action states that "...the state of the art is such that no botulinum toxins have been utilized to treat cardiac disorders, such as bradycardia" (page 5 of the Office Action).

Respectfully, this is a improper rejection because if the art had shown use of botulinum toxins to treat cardiac disorders, such as bradycardia, and applicants' specification cited to this (non-existent) art in order to meet the standard of enablement requested by the Office Action, the claims would be anticipated.

Applicant cannot be held to a standard of enablement which can be meet only by providing anticipatory prior art, and because the rejection of the claims under section 112(1) is based upon the wrong and an impossibly high test for enablement, the rejection should be withdrawn.

C. The Office Action states that five "complications have been associated with botulinum toxin therapy" (page 5 of the Office Action). These same five facts are repeated on pages 7-8 of the Office Action as allegedly showing the "unpredictability of the effects of botulinum toxin in a subject."

The five alleged complications are:

1. antibodies can develop to type A toxin;

2. a lack of alternate botulinum toxin serotypes to use;

3. the toxin can diffuse to neighboring muscles;

4. lack of consistency and low specific activities of certain toxin preparations, and;

5. the need for repeated injections of toxin to treat chronic disorders

These five "complications" appear verbatim and were taken by the Office Action from page 566 of Johnson E. A., *Clostridial Toxins as therapeutic agents: benefits of nature's most toxic proteins*, Annual Review of Microbiology, 1999, 53:551-575.

It is important to note that this Johnson article was published in a microbiology journal (Annual Review of Microbiology), not in a medical journal, and that the author Eric Johnson is a microbiologist, not a physician; see the attached four page resume of the author Eric Johnson, as published at http://www.wisc.edu/fri/ericjohn.htm.

Hence the journal in which the Johnson article was published is not to medical or clinical journal and the author, Eric Johnson, is not a physician, and therefore he has not and cannot treat patients with any affliction for any purpose. The author of the Johnson therefore has no direct experience with any of the five complications alleged to arise from use of a botulinum toxin in humans.

In the prior response submitted to the Office applicant submitted articles from peer reviewed medical journals showing that botulinum toxin has been used therapeutically in thousands of patients since about 1978 in clinical settings to safety and effectively treat many different target tissues including various spastic muscles, dystonia, pain, inflammatory disorders, excessive sweating, achalasia, anal fissure, and headache.

Furthermore, and as a supplement to what is set forth in the paragraph above, it is important to note that in **1989** the FDA approved botulinum toxin type A for the treatment of blepharospasm and strabismus, that in 2000 the FDA approved **both botulinum toxins types A and B** for the treatment of cervical dystonia and that in 2002 the FDA approved botulinum toxin type A to treat certain facial wrinkles (see the attached three pages printed out from the FDA web site located at http://www.fda.gov/cber/products/). Physicians therefore have extensive experience with the use of botulinum toxins and the FDA has explicitly approved several botulinum toxins to treat various afflictions.

Thus, with regard to the five complications set forth by the Office Action: (1) if antibodies were to develop to a type A toxin at least one alternate and FDA approved alternate toxin serotype is available (see the paragraph above); (2) hence, with regard to the second alleged complication, there is not a lack of alternate botulinum toxin serotypes to use; (3) the issue of the toxin diffusing to neighboring muscles has been easily addressed by practitioners by simply adjusting the amount of toxin used - see e.g. page S73 (right hand side column) of Berardellu A., et al., *Pathophysiology and treatment of Cranial Dystonia*, Mov

Disord 2002 Jan 21;17 (Supp 2): S70-S74 (copy attached); (4) the alleged problem of "lack of consistency and low specific activities of certain toxin preparations" seems to be non-existent or a historical issue in light of the FDA approvals (meaning that the approved toxins are both safe and effective) of several toxin serotypes, and; (5) the fact that there may be need for repeated injections of toxin to treat chronic disorders is a non sequitar: many, if not all, pharmaceuticals require at least some repeat dosing in order to treat a chronic condition and this is not a bona fide basis upon which to reject the claimed invention.

D. The Office Action rejected the present invention on the basis that it is "unpredictable and complex" since the invention "may not necessarily treat bradycardia" when "any botulinum toxin" is administered by intrapericardial injection (first paragraph on page 6 of the Office Action). The Office Action provides no authority or evidence to support this assertion, other than possibly the Johnson and Lamanna references which are discussed in section G. below.

Applicant has now submitted two declarations from a noted cardiologist which state "In my opinion this patent application provides sufficient disclosure and teaching so that a cardiologist of ordinary skill can successfully treat bradycardia by administration of a botulinum toxin into an existing pericardial space of a human patient..." (paragraph 6 of the November 5, 2001 Longhurst declaration, and paragraph 1 of the March 27, 2002 Longhurst declaration).

Respectfully, the examiner, being neither a physician nor a cardiologist, is not qualified to substitute her opinion for that of the declarant and the rejection should therefore by withdrawn.

E. The Office Action states that the specification of the instant application does not disclose any methods or working examples. (page 7 of the Office Action).

Applicant is not required to provide working examples in the application. It is well established case law that a specification need not contain working examples if, coupled with information known in the art, the invention is otherwise disclosed in the specification in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation (In re Borkowski and Van Venrooy, 164 USPQ 642 (CCPA 1970)). At least in view of the disclosure of Examples 1 to 3, and the detailed description in general, one skilled in the art would have been able to practice the claimed methods without an undue amount of experimentation.

Applicant submits that a cardiologist with ordinary skill in the art, having been taught: 1) human gross anatomy; 2) pathophysiology of neuromuscular diseases; 3) cardiac surgical techniques; and 4) pharmacology of botulinum toxins, would be able to use applicant's teaching to treat bradycardia by intrapericardial administration of a botulinum toxin.

In the present case, applicant has disclosed, by example, detailed methods for intrapericardial administration of a botulinum toxin to treat bradycardia. Furthermore, Applicant has disclosed how to inject the toxin, where to inject the toxin, appropriate formulations for the toxin and the range of the toxin dose to use. Following the detailed instructions provided by applicant it is a simple and routine matter for one skilled in the art to determine the particular dose to use with a particular patient.

As acknowledged by the Examiner, the determination of undue experimentation in connection with the claimed invention involves a balancing of the factors enumerated in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). These factors include: 1) the quantity of experimentation necessary; 2) the amount of guidance presented; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in

the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims.

Applicant respectfully submits that the "Forman factors" have been met by applicant's disclosure, for the reasons set forth below:

E1. THE QUANTITY OF EXPERIMENTATION NECESSARY

Applicant's use of a well known drug, well known drug administration method (intrapericardial) and use of the well known botulinum toxins, provide sufficient guidance for a skilled artisan to practice he claimed method. Given the teachings of the instant application, one skilled in the art would readily be able to determine the appropriate patient specific dose of toxin to use, would be access the pericardial sac to reach the site of administration for the toxin, inject the toxin, and determine whether the administration was effective. Accordingly, the specification provides the requisite guidelines to practice the invention without undue experimentation. While some additional effort may be required to optimize the claimed methods in the context of determining the optimal dosage or therapeutic schedule for bradycardia patients of different weights and states of health, such refinements would be provided during clinical trials and are not required for enablement of the claimed invention.

E2. THE AMOUNT OF DIRECTION OR GUIDANCE PRESENTED

The disclosure of the instant application, as a whole, discloses that intrapericardial botulinum toxin can be used to treat bradycardia. In addition, the instant application discloses how to make and use botulinum toxins to practice the invention. For example, page16, lines 7-12 discloses how to prepare a suitable composition containing botulinum toxin and several commercial sources for a botulinum toxin within the scope of the present invention; pages 29-33 set forth precise guidance and instructions showing how and where to inject the

botulinum toxin, and the amounts of botulinum toxin to use to treat bradycardia. The examples simply provide more detail to complement the rest of the disclosure of the invention. Thus, given the disclosure of the entire specification, physicians skilled in the art can readily practice the claimed invention. Any additional adjustments that may be needed, such as adjusting dosages, would simply be to optimize the therapeutic effects of the treatment, and clearly, such optimization would be routine to persons of ordinary skill in the art, and are not necessary to enable an invention.

Indeed, the courts have held that determining proper dosage amounts for an established treatment is routine and could be adjusted to suit the needs of an individual (U.S. v. Telectronics, Inc., 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)). In addition, the specification specifically states that the quantity of toxin administered, and the frequency of administration will be at the discretion of the physician responsible for the treatment. See e.g. page 24, line 25, continuing to page 25, line 8 and page 29, lines 27-29. Although other factors may need to be considered in optimizing the treatment protocol before actual clinical use, such factors do not require consideration to satisfy enablement under 35 U.S.C. § 112, and are not requirements for patentability. Therefore, applicant respectfully contends that the specification is enabling because those skilled in the art would know how to conduct a dose response study and perform other procedures as needed to determine the appropriate amounts of botulinum toxin to be used without undue experimentation.

E3. THE PRESENCE OR ABSENCE OF WORKING EXAMPLES

Although specific examples are not required to enable an invention, as noted above, in the present application applicant has disclosed, by example, explicitly how to locate an area to be injected with a botulinum toxin and how to administer a botulinum toxin to a patient with bradycardia. See e.g. pages 29-33. Following the instructions provided by applicant, it would be a simple and routine matter for

one skilled in the art to administer a botulinum toxin into the pericardial sac to treat bradycardia.

E4. THE NATURE OF THE INVENTION

The claimed invention is a method of treating a patient with bradycardia by intrapericardial administration of a botulinum toxin. Intrapericardial administration of various drugs is known (see e.g. page 27, lines 5-24 of the specification)[1]. Thus, intrapericardial administration of a particular pharmaceutical (i.e. botulinum toxin) does not pose any undue or unknown technical difficulties.

Additionally, botulinum toxin has an extensive clinical history. Botulinum toxin has been used therapeutically in many thousands of humans since about 1978 in clinical settings to safety and effectively treat many different target tissues besides spastic or dystonic muscles, including, for example, conditions such as pain, inflammatory disorders, excessive sweating, achalasia, anal fissure, and headache and it is known that the dose of toxin to use by local administration generally corresponds to the mass of tissue to be treated (see specification at page 25, lines 6-13).

Furthermore, similar methods involving botulinum toxins are enabled. See e.g. U.S. patents numbers 6,265,379; 6,358,926; 6,139,845; 6,350,455; 6,143,306; 6,337,075; 6,261,572; 6,358,513; 6,328,977; 6,319,506, and; 6,306,403.

The nature of the present invention is to use a known drug administration method (intrapericardial) to administer a known and FDA approved

[1] E.g. Lerner-Tung MB., et al., *Pharmacokinetics of intrapericardial administration of 5-fluorouracil*, Cancer Chemother Pharmacol 1997; 40(4):318-320 (abstract previously supplied); Tomkowski WZ., et al., *Intrapericardial cisplatin for the management of patients with large malignant pericardial effusion in the course of lung cancer*, Lung Cancer 1997 Mar; 16(2-3):215-222 (abstract previously supplied), and; Maisch B., et al., *Intrapericardial treatment of inflammatory and*

pharmaceutical (botulinum toxin). Hence, these supporting or fundament aspects of the invention are known to the art and are uncontroversial.

E5. THE STATE OF THE PRIOR ART

Information about the state of the art that is relevant to the analysis of whether undue experimentation would have been required concerns, whether those skilled in the art are sufficiently familiar with the methods needed to practice the invention. As discussed by the prior art many methods for administering botulinum toxins were sufficiently well known at the time of the invention to reduce the amount of experimentation required to practice the claimed methods. For example, as disclosed in the instant specification, botulinum toxin has been administered to patients to treat dystonia, brow furrow, constipation, blepharospasm, strabismus, and spasticity. However, the art was silent as to whether a botulinum toxin could be administered intrapericardialy to effectively treat bradycardia.

E6. THE RELATIVE SKILL OF THOSE IN THE ART

There was a high level of skill in the art at the time of applicant's invention. Physicians having medical degrees and years of residential training and experience are the norm. Additionally, cardiology is a recognized medical specialty. It was well within the skill of those in art to practice the claimed invention in view of applicant's disclosure and what was known in the art. For example, the methods disclosed by applicant teach how to access the pericardium and how to administer a botulinum to achieve the desired result of treating bradycardia.

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neoplastic pericarditis guided by pericardioscopy and epicardial biopsy – results from a pilot study, Clin Cardiol 1999 Jan; 22(1 Suppl 1): 117-22 (abstract previously supplied).

Additionally, at the time of the present invention, numerous publications were available that taught physiological and biochemical properties of botulinum toxins and taught how to administer botulinum toxin to various target sites. In addition, publications have described multiple and diverse therapeutic effects mediated by botulinum toxin.

Since the skill in the art was very high, it would not have required undue experimentation on the part of the skilled artisan to administer botulinum toxin by an intrapericardial route so as to treat bradycardia. Thus, at the time of the present invention, all the separate aspects of the claimed invention were available to practice the present invention.

E7. THE PREDICTABILITY OR UNPREDICTABILITY OF THE ART

Applicant addresses in section G. below above the alleged unpredictability in the art as set forth by the Office Action and shows that the unpredictability of he art, as alleged by the Office Action is not applicable to the claimed invention. Thus, the instant application provides sufficient teaching and guidance to enable one skilled in the art to practice the invention without an undue amount of experimentation.

E8. THE BREADTH OF THE CLAIMS

Applicant's claims, as amended, are limited to a method for treating bradycardia by intrapericardial injection of a botulinum toxin to an SA or AV node of a patient with bradycardia. The breadth of the claims is commensurate with the disclosure of the application, which describes how to make and use botulinum toxin and how to administer a botulinum toxin into the pericardium in the vicinity of the SA and AV nodes of the heart, so as to treat bradycardia.

Thus, because the specification of the instant application describes the claimed invention in such a manner that one of ordinary skill in the art can practice the invention, and because the specification, including specific examples thereto which disclose that botulinum toxin may be effectively used to treat bradycardia, applicant respectfully requests the Examiner to withdraw the section 112(1) rejection.

F. The Office Action states that there is no guidance in the specification as to the safe dosage and duration of administration of any botulinum toxin to the cardiac muscle (page 7 of the Office Action).

But quite to the contrary, the specification clearly provides ample guidance in these areas. Thus, at least page 25, line 7, continuing to page 26, line 9, as well Examples 1-3 on pages 29-33 of the application provide precise guidance which the Office Action states is lacking. For example:

Page 29 of the specification, lines 22-29:

> "Secure lodgment of the needle tip within the myocardial wall is confirmed by fluoroscopy and be resistance to an operator applied slight withdrawal pressure (tugging) upon the catheter. 0.3 U/kg to 5 U/kg of BOTOX® are then injected into the myocardium and the catheter withdrawn. Right or left ventricular injection can also be accomplished from the femoral vein. The specific amount of BOTOX® administered by this intracardiac procedure depends upon a variety of factors to be weighed and considered within the discretion of the attending physician".

Page 32 of the specification, lines 2-5:

> "Intrapericardial BOTOX® 0.3 U/kg to 5 U/kg is injected through the 4-F intrapericardial catheter without rapid diffusion into the systemic circulation."

Page 32 of the specification, lines 18-20:

"A soft floppy-tip 0.025" guidewire is then advanced to the pericardial space and the needle is exchanged for an infusion catheter. Between about 0.3 U/kg and about 5 U/kg of BOTOX® is injected."

Page 33 of the specification, lines 4-14:

"The disclosed method can locally administer between about 10 U and about 300 U of the BOTOX® and preferably between about 20 U and about 200 U of the BOTOX® to or to the immediate vicinity of the cardiac muscle portion of the *in vivo* which generates or which assists in the generation of an acute or chronic episode of bradycardia. Thus, local administration of the BOTOX® to either or to both of the SA and AV nodes can be highly effective in the treatment of bradycardia. The specific unit amount of BOTOX® to locally administer depends upon a number of factors, as previously specified, including the age and health of the patient, the size of the patient's heart, the mass of arrhythmic cardiac tissue of the patient's heart to which the BOTOX® is to be locally administered, the local administration route and mechanism chosen, etc."

Furthermore, a cardiologist of ordinary skill knows how to access the pericardial space of a patient with bradycardia and knows how to inject a pharmaceutical such a botulinum toxin into the pericardial space. Importantly, the declarant has previously stated that to a cardiologist of ordinary skill "who has knowledge of the therapeutic use of a botulinum toxin" matters such as the specific time period in which the toxin should be administered or for how long and the specific dosage to use are "routine considerations" (paragraph 7. of the November 5, 2002 declaration). The Office Action has presented no evidence to contrary. Hence, this basis for the rejection by the Office Action has been overcome.

G. The Office Action alleges that there is a contradictory state of the prior art (page 8 of the Office Action) and that this is a basis for the section 112(1) rejection. This allegation by the Office Action is based upon the Johnson and Lamanna references. It has been brought out in section C. above that the Johnson reference is the opinion of a microbiologist and that the relevant

medical art is contrary. Hence, Johnson has been disposed of as a basis for this rejection.

With regard to the Lamanna reference:

Lamanna discloses (1) administration of a botulinum toxin systemically (i.e. by intravenous injection - see e.g. page71, end of the first paragraph of Lamanna), and; (b) administration of a botulinum toxin to an isolated (i.e. dennervated) heart. (see also page 71 of Lamanna). Thus, Lamanna does not disclose or suggest intrapericardial (i.e. local) administration of a botulinum toxin.

Lamanna concludes from his observations that the toxin he administered (systemically or to isolated heart preparations) acts upon the heart through a physical, as opposed to a chemical (cell receptor) mechanism. See the last sentence of the abstract on page 69, as well as page 82 of Lamanna ("...the findings fit a physical mode of action...".

A mechanism postulated for the present invention is toxin inhibition of cholinergic vagal innervation of a bradycardiac heart to thereby permit uninhibited sympathetic innervation to increase heart rate. This can be accomplished by direct intrapericardial administration of toxin to the site of vagal innervation of the heart (see e.g. page 31, lines 12-17 (Example 2) of the specification)

Importantly, Lamanna states *"Our findings...rule against the vagal nerve-SA junction as a primary site of action for the heart changes observed in our study"* (emphasis added). (last line on page 80, continuing to page 81 of Lamanna). And remember that the study by Lamanna used only systemic toxin administration or toxin administrated to an isolated (and therefore dennervated) heart preparation.

Contrarily, the present invention, as claimed, is directed to a local administration of toxin to the SA node or AV node of the heart where the vagal nerves terminate. Hence, while Lamanna is directed to a systemic administration of toxin (which may cause, as observed by Lamanna, a physical effect upon the heart), the present invention is directed to a direct SA or VA node application of toxin to the heart to thereby cause uptake of toxin by the cholinergic receptors at that location.

Hence, Lamanna is not contradictory art with regard to the present invention because the observations of Lamanna result from a different experimental protocol. He used systemic or isolated heart toxin application, while applicant uses intrapericardial administration to the SA or AV nodes of the heart.

To further distinguish Lamanna from the present invention, all claims have been amended to limit the site of administration of the botulinum toxin "to an SA node or to an AV node of a heart of a patient with bradycardia"

Intrapericardial administration of a botulinum toxin according to the present invention is carried out so as to avoid entry of the botulinum toxin into the systemic circulation (see e.g. page 25, lines 2-5 of the present specification). Systemic administration of significant amount of a botulinum toxin can be expected to be very harmful or fatal in humans – the therapeutic uses of a botulinum toxin are all by local administration (i.e. subcutaneous, intramuscular or intraglandular), not by any systemic (i.e., intravenous) route. It is for this reason that the present claims are all directed to a particular local administration route for the toxin – by an intrapericardial route (i.e. into the pericardial sac which surrounds the heart).

Additionally, Lamanna's administration of a botulinum toxin to an isolated heart also has no relevance to the claimed invention. Applicant's specification at page 1, lines 15-16, page 24, lines 7-18 and at page 25, lines 3-5 discloses that

the vagus (parasympathetic) nerve innervates the heart, and that bradycardia can be treated by the action of a botulinum toxin upon the vagal ending in the heart without entry of the botulinum toxin into the systemic circulation. Note as set forth at page 1, lines 17-18 of the specification that "Heart rate can be increased by sympathetic stimulation and decreased by vagal stimulation." Thus, a proposed mechanism for the efficacy of the present claimed invention is inhibition of vagal (parasympathetic, cholinergic) activity by intrapericardial (direct, local) administration of a botulinum toxin. Down regulation of vagal activity thereby permit the unaffected sympathetic (adrenergic) innervation of the heart to reduce or eliminate the bradycardia. The isolated heart preparation of Lamanna is a denervated heart.

Hence, both the systemic toxin administration (strongly contraindicated in humans – since this would cause botulism)) and the "vagotomy" (isolated) heart preparation used by Lamanna *have no applicability to the present invention.* Hence, the observations in the Lamanna reference are of little or no relevance to the present claimed invention.

In other words, Lamanna does not teach or suggest that **intrapericardial** administration of a botulinum toxin is unpredictable or will have unexpected results. Lamanna may very well have observed bradycardia upon his systemic administration of a toxin because he used a **systemic** route of toxin administration, which assures wide spread effects based upon different physiological mechanisms.

For these reasons the section 112(1) rejection of claims 7-11, 14-18 and 28-34, as amended, should be withdrawn.

V. Re-Submitted IDS